Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

The amendment to the specification is made to correct three typographical errors appearing in the amended paragraph. The amendments to SEQ ID NO: 8 and SEQ ID NO: 12 find descriptive support in SEQ ID NO: 1 as filed. The remaining amendment harmonizes the span of the residues appearing in SEQ ID NO: 17 to the corresponding sequence within SEQ ID NO: 1. Therefore, no new matter has been entered. Accompanying this amendment is a corrected Sequence Listing, along with a diskette containing the computer readable form, and a Statement Under 37 CFR § 1.821.

The rejection of claims 68-70 and 73-76 under 35 U.S.C. § 112 (first paragraph) as containing new matter is respectfully traversed. To be considered new matter, the recitation of the limitation "SEQ ID NO: 16 or 17" must lack written descriptive support in the specification as filed. *See In re Rasmussen*, 650 F.2d 1212, 1214-15, 211 USPQ 323, 326 (CCPA 1981). Compliance with the written description requirement does not require *in haec verba* recitation of the language in the specification. *See In re Wright*, 866 F.2d 422, 425, 9 USPQ2d 1649, 1651 (Fed. Cir. 1989). Instead, the specification need only communicate that applicants were in possession of the subject matter as presently claimed. *Utter v. Hiraga*, 845 F.2d 993, 998, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988). The specification of the present application does, indeed, demonstrate possession of the presently claimed subject matter.

At page 16, lines 24 and 25, SEQ ID NOS: 16 and 17 are identified as being domains of biliverdin reductase ("BVR") that possess protein kinase C ("PKC") enhancing and inhibiting activities, respectively. These sequences are each generic (i.e., containing Xaa residues symbolic of any amino acid). At page 17, lines 22-23, the specification indicates that fragments of BVR preferably contain one or more of the above-listed functional domains, and possess one or more activities of the full-length BVR. On page 18, lines 17-28, the specification identified two species, SEQ ID NOS: 18 and 34, that are encompassed by the generic sequence of SEQ ID NO: 16; as well as two species, SEQ ID NOS: 19 and 35, that are encompassed by the generic sequence of SEQ ID NO: 17. On page 27, lines 27-30, C-terminal polypeptide fragments of BVR are identified as being useful as inhibitors of PKC activity and SEQ ID NOS: 19 and 35 are particularly identified. On page 28, line 31 to page

29, line 6, internal polypeptide fragments of BVR are identified as being useful as enhancers of PKC activity and SEQ ID NOS: 18 and 34 are particularly identified. Thus, one of ordinary skill in the art would fully appreciate that SEQ ID NOS: 18, 19, 34, and 35 are only preferred polypeptide fragments of BVR that can inhibit or enhance PKC activity, and that the present application fully contemplates use of all sequences containing generic SEQ ID NOS: 16 or 17 in the method as presently claimed. Based on the foregoing, it is evident that no new matter has been entered.

For these reasons, the rejection of claims 68-70 and 73-76 as containing new matter is improper and should be withdrawn.

The rejection of claims 68-77 under 35 U.S.C. § 112 (first paragraph) as lacking written descriptive support is respectfully traversed.

The U.S. Patent and Trademark Office ("PTO") has taken the position that the claimed invention lacks written descriptive support for three reasons: (i) the disclosed species of rat and human BVR are insufficient to provide descriptive support for "mammalian" BVR; (ii) the identification of a consensus sequence for fragments of BVR that possess PKC inhibitory activity and fragments of BVR that possess PKC stimulatory activity, as well as the identification of individual species thereof is insufficient to provide descriptive support for fragments possessing the consensus sequences of SEQ ID NO: 16 or 17; and (iii) PKC isozymes other than human α, β, and γ isozymes. Because of the amendments introduced to the claims, the latter basis is rendered moot and therefore only the first and second bases are addressed below.

First Basis of Rejection

The basis asserted by the PTO for rejection of the claim language "mammalian" BVR is that because some proteins (in particular, proteins other than BVR) can have distinct functions lost or modified with only slight changes in the amino acid sequence, applicant's description of three species of the genus of mammalian BVR is insufficient. Applicant disagrees with the PTO's position.

As noted by applicant in the prior response, the present application identifies three species of mammalian BVR, two from human and one from rat; identifies BVR functional domains at page 16, lines 8-33; describes preparation of BVR fragments and identifies exemplary fragments at page 17, line 22 to page 18, line 28; and describes preparation of BVR variants and identifies exemplary variants at Example 1 and at page 18, line 29 to page 19, line 24. In addition, the specification recites at page 27, lines 15-23, that

preferred inhibitors of PKC activity are polypeptide fragments of BVR that include a C-terminal fragment of rBVR or hBVR, and at page 27, line 31 to page 28, line 6, that preferred enhancers of PKC activity are polypeptide fragments of BVR that include an internal fragment of rBVR or hBVR. Specific examples of the former include SEQ ID NOS: 19 and 35; specific examples of the latter include SEQ ID NOS: 18 and 34. Example 3 describes the demonstration of these polypeptide fragments of BVR that possess PKC regulatory activity.

Applicant submits that the demonstration of conservation among rat and human BVR would have allowed one of ordinary skill in the art to conclude that applicant was in possession of the presently claimed invention, because the present application sets forth three species within the scope of the recited genus, identifies structural features characteristic of mammalian BVR, *and* identifies the structural regions of BVR that will act as inhibitors or enhancers of PKC activity. That the present application supports the claim language 'mammalian BVR' is entirely consistent with the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement, 66 Fed. Reg. 1099 (January 5, 2001) ("Written Description Guidelines"), because the present application describes both "a representative number of species" and discloses "structural or other physical and/or chemical properties" (as well as a correlation between structural and functional properties).

The burden of establishing that an application lacks adequate written descriptive support falls on the PTO. *See In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("[T]he PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims."). In this case, the only assertion made by the PTO to support its conclusion is that the function of proteins, generally, cannot be predicted exclusively based on structural homology (*see* page 5 of office action). Thus, the PTO presents only *indirect* evidence that the three disclosed species may or may not be representative of the recited genus, while the present application presents *direct* evidence of the structural and functional features shared by the three exemplary members of the recited genus (which, applicant submits, would allow one of ordinary skill in the art reasonably to conclude that applicant was in possession of the recited genus). Despite the overwhelming evidence that the three disclosed species appear to share identical hydrophobic domains, identical nucleotide binding domains, identical oxidoreductase domains, conserved leucine zipper domains, conserved kinase motifs, identical nuclear localization signals, identical myristylation sites, conserved zinc finger domains, conserved PKC enhancing domains, and conserved PKC inhibiting

domains (*see* page 16, lines 8-33), the PTO concludes that this is insufficient given its previously asserted *indirect* evidence.

Nowhere has the PTO presented evidence that the three species of mammalian BVR are *not* representative of the recited genus, as required by *In re Wertheim*. Instead, the PTO has taken the position that three species is simply inadequate given the size of the recited genus. The Written Description Guidelines indicate that when the genus represents widely variant species more than one species is required, yet when the genus represents closely related species as few as one species may be sufficient. 66 Fed. Reg. at 1106. Thus, size of the genus is clearly of less import than variance of species within the genus. In this case, the *direct* evidence presented in the specification demonstrates that structural and functional variance is at a minimum. The PTO, in sharp contrast to applicant, has provided no evidence concerning variance within the genus.

In addition to the foregoing and as further support for the fact that the three species *are* representative of the recited genus of mammalian BVR, enclosed herewith is a declaration by Mahin Maines under 37 C.F.R. 1.132 ("Maines Declaration"). The Maines Declaration demonstrates that the structure and function of BVR proteins are highly conserved among mammalian BVR and, therefore, results achieved with human and/or rat BVR are predictive of results that can be achieved with other mammalian BVR (Maines Decl. ¶ 4).

The present application identifies two human BVR amino acid sequences (SEQ ID NO: 1 and SEQ ID NO: 3) and a single rat BVR amino acid sequence (SEQ ID NO: 4) (Maines Decl. ¶ 5). The two human BVR sequences are 99 percent identical (*Id.*). The human BVR of SEQ ID NO: 1 and the rat BVR of SEQ ID NO: 4 are 82 percent identical (*Id.*). Mammalian BVR proteins are characterized by a number of shared structural features (*see* Maines Decl. ¶ 6). In comparing the human BVR sequence of SEQ ID NO: 1 and the rat BVR sequence of SEQ ID NO: 4, the rat sequence contains an identical hydrophobic domain, an identical nucleotide binding domain, an identical oxidoreductase domain, a conserved leucine zipper domain (i.e., with any residue variations being between L and K residues), identical or conserved kinase motifs, an identical nuclear localization signal, an identical myristylation site, a conserved zinc finger domain, a conserved PKC enhancing domain, and a conserved PKC inhibiting domain (*Id.*). Based on the shared or conserved structural features between the human and rat BVR sequences, one of ordinary skill in the art would expect other mammalian BVR sequences to share these same identical or conserved structural features (*Id.*).

The reasonableness of the expectation of shared structural features, based on a comparison of human and rat BVR sequence, is confirmed by the alignment of human and rat BVR sequences with the mouse and pig BVR sequences, which have subsequently been obtained in Dr. Maines' laboratory (*see* Maines Decl. ¶ 7). The mouse and pig BVR amino acid sequences were aligned with the human and rat BVR amino acid sequences using the ClustalW alignment program set on its default settings (*Id.* and Exhibit 3 thereto). The mouse BVR sequence is about 81 percent identical to the human BVR sequence of SEQ ID NO: 1 (Maines Decl. ¶ 8). Based on the alignment shown as Exhibit 3 to the Maines Declaration, one of ordinary skill in the art would conclude that mouse BVR, when compared to the human BVR of SEQ ID NO: 1, contains an identical hydrophobic domain, an identical nucleotide binding domain, an identical oxidoreductase domain, a conserved leucine zipper domain (i.e., with any residue variations being between L and K residues), identical or conserved kinase motifs, a conserved nuclear localization signal, an identical myristylation site, a conserved zinc finger domain, an identical PKC enhancing domain, and a conserved PKC inhibiting domain (*Id.*). This high structural conservation, particularly within previously identified functional domains of the protein, indicates that the proteins are functionally quite similar (*Id.*). The pig BVR sequence is about 98 percent identical to the human BVR sequence of SEQ ID NO: 1 (Maines Decl. ¶ 9). Based on the alignment shown as Exhibit 3 to the Maines Declaration, one of ordinary skill in the art would conclude that the pig BVR, when compared to the human BVR of SEQ ID NO: 1, contains an identical hydrophobic domain, an identical nucleotide binding domain, an identical oxidoreductase domain, a conserved leucine zipper domain (i.e., with any residue variations being between L and K residues), identical or conserved kinase motifs, an identical nuclear localization signal, an identical myristylation site, a conserved zinc finger domain, an identical PKC enhancing domain, and an identical PKC inhibiting domain (*Id.*). This high structural conservation, particularly within previously identified functional domains of the protein, indicates that the proteins are functionally quite similar (*Id.*).

In addition, based on the known biochemical pathways shared by mammalian BVR proteins, one of ordinary skill in the art would have expected the results achieved with one mammalian BVR to be consistent with other mammalian BVR (Maines Decl. ¶ 10). Prior to the present application, it was widely believed that BVR was a general housekeeping enzyme that was conserved among mammals, catalyzing the NADPH-dependent reduction of biliverdin to produce bilirubin (*Id.*). In particular, Noguchi et al., "Purification and Properties of Biliverdin Reductase from Pig Spleen and Rat Liver," *J. Biochem.* 86(4):833-848

(1979)("Noguchi")(copy attached as Exhibit 6 to the Maines Declaration) reports that purified pig and rat BVR has both NADH- and NADPH-dependent activities in converting biliverdin to bilirubin, with the NADH-dependent activity being optimal at pH 6.9 and the NADPH-dependent activity being optimal at pH 8.5 (*Id.*). Noguchi also indicates that both systems are inhibited by bilirubin, but inhibition of the NADPH-dependent activity was more pronounced (*Id.*). In addition, Noguchi reports that the NADPH-dependent activity for biliverdin had a K_m of 0.3 μM whereas the NADH-dependent activity for biliverdin had a K_m of 1-2 μM (*Id.*). Rigney et al., "The Reaction Mechanism of Bovine Kidney Biliverdin Reductase," *Biochim. Biophys. ACTA* 957:237-242 (1988)(copy attached as Exhibit 7 to Maines Declaration) reports that purified bovine BVR has both NADH- and NADPH-dependent activities in converting biliverdin to bilirubin, with the NADH-dependent activity being optimal at pH between 6 and 7 (depending on the buffer system utilized) and the NADPH-dependent activity being optimal at pH 8.5 (*Id.*). Rigney et al., "The Kinetics of Ox Kidney Biliverdin Reductase in Pre-steady State: Evidence That the Dissociation of Bilirubin is the Rate-determining Step," *Biochem J.* 259:709-713 (1989)(copy attached as Exhibit 8 to Maines Declaration) confirms that the broad features of the reaction mechanism for NADPH- and NADH-dependent activities are the same, with BVR activity exhibiting a pH-dependent burst in the rate of conversion of biliverdin to bilirubin followed by a steady-state rate (*Id.*). As addressed in the present application, at Example 1, human BVR shares the property of dual co-factor activity using NADPH and NADH (*Id.*). In addition to the conserved activity among mammalian BVR, Rigney et al., "Some Physical and Immunological Properties of Ox Kidney Biliverdin Reductase," *Biochem J.* 255:431-435 (1988)(copy attached as Exhibit 9 to Maines Declaration) reports that antibodies raised against ox BVR were able to immunoprecipitate BVR from numerous mammals, including pig, guinea pig, mouse, rat, hamster, fox, wallaby, and human (*Id.*). All of the foregoing confirms that those persons of skill in the art believed BVR to be functionally well-conserved among mammals (*Id.*).

Thus, based upon the high degree of structural similarity of the three BVR proteins identified in the present application, as confirmed by their high degree of structural similarity with mouse and pig BVR sequences, and the functional similarity of many mammalian BVR proteins, persons of skill in the art would have expected results achieved with any one mammalian BVR protein to be achievable with other mammalian BVR proteins (Maines Decl. ¶ 11).

In view of all of the foregoing, applicant submits that one of ordinary skill in the art would have undoubtedly appreciated that applicant was in possession of the claimed subject matter. Therefore, the first basis for the rejection of claims 68-77 is improper.

Second Basis of Rejection

With respect to the finding of no written descriptive support for fragments of BVR that contain the consensus sequences of SEQ ID NO: 16 or 17, applicant respectfully submits that the PTO position is without basis. The PTO suggests at page 5 of the outstanding office action that no disclosure of PKC regulatory activity of SEQ ID NOS: 16 or 17 could be found in the specification. Applicant respectfully submits that this statement is erroneous. As noted above, SEQ ID NOS: 16 and 17 are generic or consensus sequences. Each therefore represents a subgenus of polypeptide fragments of BVR that can modify PKC activity. As noted above, Example 3 provides ample evidence that two species of each disclosed subgenus have such regulatory activity. This is sufficient to establish written descriptive support for the subgenus of polypeptide fragments of BVR that comprise SEQ ID NO: 16 or 17. *See Ex parte Sorenson*, 3 USPQ2d 1462 (Bd. Pat. App. & Interf. 1987) (identification of subgenus and species falling within the subgenus were sufficient to satisfy the written description requirement). For these reasons and the reasons noted above in response to the new matter rejection, applicant submits that the second basis for rejection of claims 68-77 is improper.

In view of all of the above, the rejection of claims 68-77 under 35 U.S.C. § 112 (first paragraph) as lacking written descriptive support is improper and should be withdrawn.

The rejection of claims 68-77 under 35 U.S.C. § 112 (first paragraph) for lack of enablement is respectfully traversed in view of the above amendments and the following remarks.

Applicants have amended the language of claim 68 to recite that the PKC is "human protein kinase C selected from the group of isozymes α, β, and γ...". Therefore, all of bases of rejection concerning the PKC whose activity is modified in accordance with the recited method is overcome by such amendments. The only remaining bases of rejection concern: (i) enablement for the use of mammalian BVR other than the specific sequences recited in the specification; and (ii) any fragments of mammalian BVR with PKC regulatory activity other than those of SEQ ID NOS: 18, 19, 34, and 35.

With respect to the first basis of rejection, to the extent that the PTO again relies on *indirect* evidence that the three disclosed species may or may not be representative of the recited genus, applicant relies on the foregoing demonstration as evidence that the three disclosed species *are* representative of the recited genus of mammalian BVR. Given the *demonstrated* conservation of function and structure between different species of mammalian BVR, one of ordinary skill in the art would expect that results achieved with one or more species of mammalian BVR would be predictive of success using other species of mammalian BVR.

In addition to the foregoing, applicant would like to point out that the PTO erroneously concludes at page 7 of the outstanding office action that "[n]o disclosure of the critical structural elements required in a mammalian polypeptide to display BVR reductase activity has been provided." While applicant believes it is not necessary for one of ordinary skill in the art to make such a demonstration, applicant submits that the present application nonetheless defines the structural features required for BVR reductase activity in Example 1. In particular, at page 54, lines 5-11, the specification recites:

> Data suggest that certain residues in conserved phosphate binding motifs are of significance to display of the unique character of the enzyme. Residues, such as Cys^{74}, Cys^{281} and Lys^{92}/His^{93} in the "oxidoreductase" domain, are required for activity at both pH/cofactor settings, and their absence effects activity at both experimental settings to the same extent. The "oxidoreductase" motif (SEQ. ID. No. 8) is found conserved among oxidoreductases, including both the procaryotic and eukaryotic species. *Thus, these data should be broadly applicable to other BVR.*

(emphasis added). From the foregoing excerpt appearing in Example 1, the present application does clearly identify the structural requirements for oxidoreductase activity.

The PTO also improperly concludes at pages 7-8 of the outstanding office action that there is no discussion of which domains of mammalian BVR are needed for PKC modulating activity other than SEQ ID NOS: 34 and 19. For substantially the same reasons noted above, applicant submits that the present application sufficiently enables one of ordinary skill in the art to practice the invention using polypeptide fragments of BVR that comprise SEQ ID NO: 16 or 17. The PTO asserts that there is no disclosure of size requirement for polypeptide fragments of BVR. Applicant submits that such disclosure is not necessary. For example, Example 3 results demonstrate that both full length rat BVR (containing SEQ ID NO: 18), a fragment thereof consisting of SEQ ID NO: 18, and a

fragment of human BVR consisting of SEQ ID NO: 34 demonstrated activity enhancing PKC activity. Because both full length rat BVR and the polypeptides of SEQ ID NO: 18 and 34 possess the same activity, it is reasonable for one of ordinary skill in the art to expect that other polypeptide fragments that contain SEQ ID NO: 16 would possess similar PKC activity.

For all these reasons, the rejection of claims 68-77 under 35 U.S.C. § 112 (first paragraph) for lack of enablement is improper and should be withdrawn.

The rejection of claims 69-75 and 77 under 35 U.S.C. § 112 (first paragraph), lack of enablement with respect to *in vivo* performance of the claimed method is respectfully traversed.

The PTO has asserted that the present application fails to provide sufficient enablement for *in vivo* use of BVR or fragments thereof that can regulate (i.e., enhance or inhibit) protein kinase C activity. The basis of this rejection is the lack of experimental data in the specification evidencing *in vivo* success.

Initially, applicant would like to point out that *in vivo* experimental data is not a requirement for enablement an invention. *See In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Long*, 368 F.2d 892, 895, 151 USPQ 640, 642 (CCPA 1966). All that is needed is objective enablement of what is claimed. *In re Wright*, 999 F.2d at 1561, 27 USPQ2d at 1513.

Applicant submits that *in vivo* experimental data is not required for the presently claimed invention, because the present claims do *not* require a particular treatment to be effected. That is, a specific result of such PKC regulation is not recited in the presently claimed invention. The claims are merely directed to the regulating of PKC activity, whether such regulation occurs *in vitro* or *in vivo*. Applicant has demonstrated that PKC activity can be regulated *in vitro* and stated that such regulation can likewise occur *in vivo*, but the PTO contends that the *in vitro* success cannot be correlated to *in vivo* success. Applicant disagrees, because applicant has previously submitted evidence that a correlation does exist between PKC regulation *in vitro* and PKC regulation *in vivo* (*see* Hara et al., *J. Cereb. Blood Flow Metab.* 10:646-653 (1990) (copy attached as Exhibit A to August 20, 2002 response); Meyer et al., *Int. J. Cancer* 43:851-856 (1989) ("Meyer") (copy attached as Exhibit B to August 20, 2002 response)). Meyer, in particular, demonstrates the correlation between *in vitro* inhibition of PKC activity with *in vivo* inhibition of PKC activity using intraperitoneal administration of a protein kinase C inhibitor (designated CGP 41 251) to contact bladder carcinoma xenografts in athymic nude mice (*see* Meyer at page 853). Given that PKC has

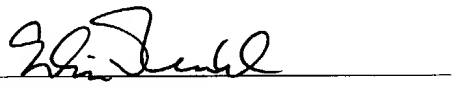
previously been demonstrated to interact with compounds that regulate its activity both *in vitro* and *in vivo*, one of ordinary skill in the art would expect other *in vitro*-demonstrated regulators of PKC activity to behave similarly *in vivo* (i.e., they will likewise regulate PKC activity *in vivo*).

Given the results of Meyer and Example 3 of the present application, as well as the fact that the claims do not recite a particular result of regulating PKC activity, one of ordinary skill in the art would fully expect that mammalian BVR and fragments thereof with PKC regulatory activity would be able regulate PKC activity when administered *in vivo*. The PTO does not appear to contest the enablement of delivering mammalian BVR or fragments thereof with PKC regulatory activity for purposes of practicing the claimed invention. Therefore, the rejection of claims 68 and 69-75 for lack of enablement is improper and should be withdrawn.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: March 3, 2004



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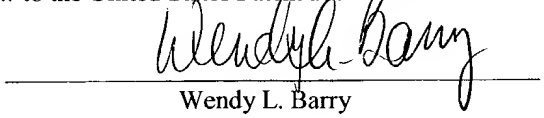

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